REMARKS

Summary of Interview

The Examiner is thanked for the courtesy of the telephonic interviews with Applicants' undersigned representative on November 7, 2005. During that interview the prior art and 35 USC 103 rejections were discussed. The Examiner agreed that cited art does not teach or suggest providing a set of candidate three-dimensional conformations for the protein's primary sequence; and applying physical distance constraint to the candidate three-dimensional conformations. The Examiner indicated that pending further reflection the 35 USC 103 rejections would be withdrawn. The 35 USC 112, second paragraph rejection was also discussed and the Examiner agreed that the amendments to claim 1 would be sufficient to overcome this rejection.

Pending claims

Claims 1, 5, 8-14, 21-24 and 75-82 are pending. Claims 1, 8 and 78 been amended to add that the tertiary structure of the protein is determined by selecting one or more of the three-dimensional conformations.

No new matter has been added.

The Rejections Under 35 USC 112, Second Paragraph

Claims 1, 5, 8-14, 21-24 and 75-82 are rejected under 35 USC 112, second paragraph. Specifically, the Examiner has rejected independent claims 1, 8, 78 as being indefinite for reciting "a method of determining the tertiary structure of the protein" without a final step of determining the tertiary structure. Applicants have amended these claims to recite that the tertiary structure of the protein is determined by selecting one or more of the three-dimensional conformations.

Applicants believe these amendments overcome the rejections. Accordingly, withdrawal of the rejections under 35 USC 112, second paragraph is respectfully requested.

The Rejections Under 35 USC 103

Claims 1, 5, 8-14, 21-23 and 75-77 were rejected under 35 USC 103(a) as being unpatentable over Lacroix et al., Biochemistry (1997), Vol. 36, pages 6270-

6282 ("Lacroix") in view of Mitra et al., Journal of the American Chemical Society (1979), Vol. 101, pages 3097-3110 ("Mitra"), and further in view of Havel et al., Biopolymers (1979), Vol. 18, pages 73-81 ("Havel"). The Examiner states that Lacroix shows hypothetical structures of the peptides with predicted protein folds in Figures 9-11 and that the homology modeling is similar to that of Rossi et al ("Rossi"). The Examiner states that while Lacroix does not teach imposing distance constraints on candidate conformations, Mitra discloses "general techniques for establishing the tertiary structures of proteins based on cross-linking reagents" and that one of ordinary skill would have been motivated to combine the protein structure determination of Lacroix with the cross-linking reagents as taught in Mitra.

As has been discussed in the previous Amendments, the present invention employs the combination of the following steps to determine the tertiary structure of a protein:

A. providing a set of candidate three-dimensional conformations for the protein's primary sequence; and

B. applying physical distance constraint information associated with the cross-linking for the identified cross-link fragments to the candidate three-dimensional conformations to rank said three-dimensional conformations and selecting one or more of said three-dimensional conformations based on the rankings.

As discussed in the November 7, 2005 interview and further below, none of the cited references, alone or in combination, teach or suggest the combination of steps A and B.

Lacroix describes positioning whole domains (of fixed conformation) of the γ-B protein region with respect to one another. The catalytic region of the Clr serine protease is a homodimer of two γ-B monomers. These γ-B monomers are posited to contain relatively large discrete domains or CCP modules. Lacroix shows the assembly of the domains or modules of the γ-B monomer and the $(\gamma\text{-B})_2$ dimer of the protein region by chemically cross-linking the $C1r(\gamma\text{-B})_2$ dimer and performing modeling studies.

As pointed out in the specification of the present patent application, the Lacroix (as well as the related Rossi et al. reference) shows that "domain-domain placement can be done" using intra-molecular cross-linking. See page 10, lines 8-14 of the instant specification. What these references do not suggest is use of cross-linking and subsequent analysis as claimed to determine a tertiary structure of the

polypeptide. Lacroix uses two cross-links to merely propose, roughly, the relative positions of multiple "pre-built" domains of $(\gamma\text{-B})_2$ dimer. These proposed relative positions are what are shown in Figures 9-11.

Thus, Lacroix does not propose a set of candidate three-dimensional conformations for the protein's primary sequence as required by step A of the present claims. Nor does Lacroix suggest selecting one or more candidate conformations for the protein under consideration by applying distance constraint information (obtained from the cross-link data) to the candidate conformations as required by step B. Lacroix applies cross-link data only to whole domains (of fixed conformation) to position those domains with respect to one another.

Neither Mitra nor Havel suggest the claimed features that are lacking in Lacroix. Mitra teaches reagents for cross-linking proteins. As discussed in previous Amendments, Lacroix teaches producing intra-monomer cross-links, and then using this cross-link information was used in conjunction with homology modeling to position the domains of the γ-B monomer with respect to one another, thereby constructing a three-dimensional model of the γ-B monomer.

Combining the cross-linking reagents taught in Mitra with the method of protein structure determination of Lacroix would not result in the claimed invention. Rather, it would result in using the cross-linking reagents taught in Mitra to produce intra-monomer cross-links (within a single γ-B) and inter-monomer cross-links (between the individual residues of the separate γ-B monomers in a $(\gamma\text{-B})_2$ dimer) as taught in Lacroix.

Havel describes using basic distance geometry to solve for structures which satisfy the geometry. However, Havel does not suggest providing a set of candidate three-dimensional conformations for the protein's primary sequence; and then applying physical distance constraint information associated with the cross-linking for the identified cross-link fragments to the candidate three-dimensional conformations.

Thus, Applicants submit that independent claims 1, 8 and 78 are patentable over the prior art. As all independent claims are patentable over the cited art, the dependent claims are patentable as well. Therefore withdrawal of the rejections of claims 1-3, 5, 8-14, 21-24 and 75-77 is respectfully requested.

Conclusion

Applicants respectfully submit that all pending claims are allowable and respectfully requests a Notice of Allowance for this application from the Examiner. If the Examiner wishes to telephone the applicants representative concerning any matter pertaining to this case, the Examiner is cordially invited to do so at the telephone number set out below. The Commissioner is hereby authorized to charge any additional fees to Deposit Account 500388 (Order No. UCSFP001).

Respectfully submitted,
BEYER WEAVER & THOMAS, LLP

Denise Bergin
Registration No. 50,581

P.O. Box 70250
Oakland, CA 94612-0250